Natural Products Synthesis

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Sulfone-Mediated Total Synthesis of (±)-Lepadiformine**

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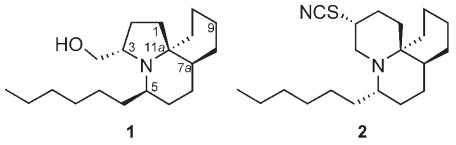
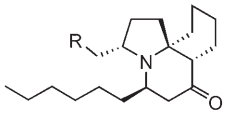
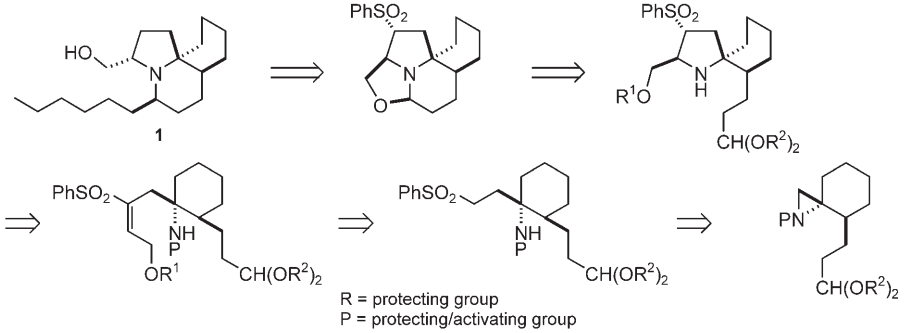
(−)-Lepadiformine (**1**) is a decahydro-1*H*-pyrrolo[1,2-*j*]quinoline isolated in 1994 by Biard et al. from the tunicate *Clavelina lepadiformis*.[1] Lepadiformine has moderate in vitro cytotoxic activity towards various tumor cell lines, including non-small-cell lung carcinoma (NSCLC-N6), and is also a cardiac-K^+-channel blocker.[2] Lepadiformine is related both biologically and structurally to the marine alkaloid (−)-fasicularin (**2**)[3] and the cylindricines **3**.[4] In the late 1990s, the research groups of Weinreb[5] and Pearson[6] showed independently through unambiguous total syntheses that **1** must have the 7*aR*,11*aS* relative configuration corresponding to *trans* fusion of the carbocycle to the octahydroindolizine substructure. The relative configuration of all stereocenters in structure **1** was proved by the first total synthesis of the racemic natural product, which was completed by Kibayashi and co-workers in late 1999.[7a] The same research group established the absolute configuration of **1** in 2002.[7b] To date, a further four total syntheses of racemic or enantiomerically pure **1** have been completed,[8–11] together with notable partial and total syntheses of **2**[7a,c,d,e,8d,12] and **3**.[5b,7d,10,13]





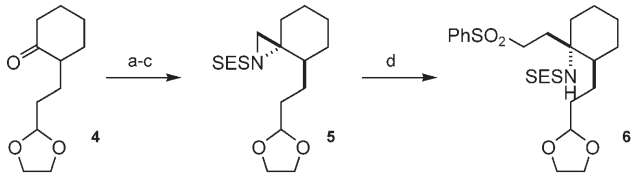
(+)-**3** R = Cl: cylindricine A
R = HO: cylindricine C
R = MeO: cylindricine D
R = AcO: cylindricine E
R = NCS: cylindricine F

Our interest in the total synthesis of lepadiformine stemmed in large part from the presence of a highly substituted pyrrolidine ring embedded in the tricyclic core. Previous studies in this laboratory resulted in total syntheses of the pyrrolidine-containing alkaloids (+)-monomorine I[14] and (+)-preussin.[15] The pyrrolidine rings were formed by base-mediated 5-*endo*-trig cyclization reactions, in which amides undergo an intramolecular reaction with vinylic sulfones generated in situ. It occurred to us that the hexyl side chain in **1** could be introduced by substitution of an aminal, which could in turn be accessed from a pyrrolidine formed through a 5-*endo*-trig cyclization of a suitably substituted vinylic sulfone (Scheme 1). We planned to make the unsaturated cyclization substrate from a spirocyclic aziridine by nucleophilic ring opening with lithiated methyl phenyl sulfone followed by condensation with an aldehyde, along the lines established in our earlier methods[16] and total syntheses.



Scheme 1. Retrosynthetic analysis of **1**.

Our synthesis started from the ketone **4** (Scheme 2),[17] which was synthesized in 99% yield by alkylation of the lithium enolate of *N*-cyclohexylidenecyclohexanamine with 2-(2-bromoethyl)-1,3-dioxolane under the conditions described by Minor and Overman.[18] The reaction of **4** with



Scheme 2. a) $Me_3S(O)I$, NaH, DMSO, 96%; b) $SESNH_2$, K_2CO_3, DMF, 85%; c) ADDP, PMe_3, THF, 95%; d) $PhSO_2Me$, *n*BuLi, THF, 97%. DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide.

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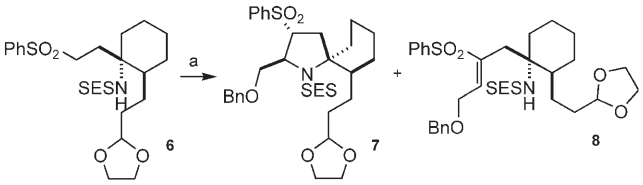
dimethylsulfoxonium methylide gave a single epoxide in good yield. This epoxide was combined with 2-(trimethylsilyl)ethanesulfonamide under mildly basic conditions[19] to give the *N*-SES (SES = 2-(trimethylsilyl)ethylsulfonyl) amino alcohol, which was subjected to modified Mitsunobu conditions (1,1′-(azodicarbonyl)dipiperidine (ADDP), Me_3P) similar to those reported by Tsunoda et al.[20] to give the spiroaziridine **5** with clean inversion of configuration at the tertiary-alcohol stereocenter. Aziridine **5** underwent nucleophilic ring opening upon exposure to lithiated methyl phenyl sulfone to provide the sulfone-containing sulfonamide **6** in excellent yield.

At this stage we intended to complete the assembly of the vinylic sulfone moiety required for the 5-*endo*-trig cyclization by the combination of **6** with protected 2-hydroxyethanal under the conditions developed during the course of our (+)-preussin synthesis (Scheme 3).[15] In the event, the treatment of the dilithio dianion of **6** with 2-benzyloxyethanal and



Scheme 3. a) *n*BuLi (2 equiv), THF, −78 °C, then $BnOCH_2CHO$, then PhCOCl, **7**: 60 %. Bn = benzyl.

quenching with benzoyl chloride gave directly the *N*-SES-protected pyrrolidine **7** in 60 % yield as a single isomer, the structure of which was determined by X-ray crystallographic analysis (Figure 1).[21] In light of our previous studies,[14,16] we conclude that compound **7** is formed by the 5-*endo*-trig cyclization of an *E* vinylic sulfone resulting from the elimination in situ of the benzoate formed when the dianion derived from **6** is quenched with 2-benzyloxyethanal and then benzoyl chloride. In support of this analysis, a substance believed to be the *Z* vinylic sulfone **8** was also obtained from this reaction in 13 % yield, although difficulties encountered in its purification precluded comprehensive spectroscopic analysis.

The completion of the total synthesis of **1** required 1) cyclization to form the piperidine, 2) introduction of the hexyl side chain, and 3) adjustment of the configuration of the carbon center at which the hydroxymethyl side chain is attached to the pyrrolidine ring. To this end, the desulfonylation of **7** with nBu_4NF and exposure of the resulting pyrrolidine to BBr_3 effected debenzylation and acetal cleavage to give the tricyclic aminal **9** in high yield for the two-step sequence (Scheme 4). Initial attempts to introduce the saturated side chain directly from **9** by using hexylmagnesium bromide were high yielding, but gave **10**, the product of the addition of the organometallic species to the lower, *Si*, face rather than to the desired upper, *Re*, face of the

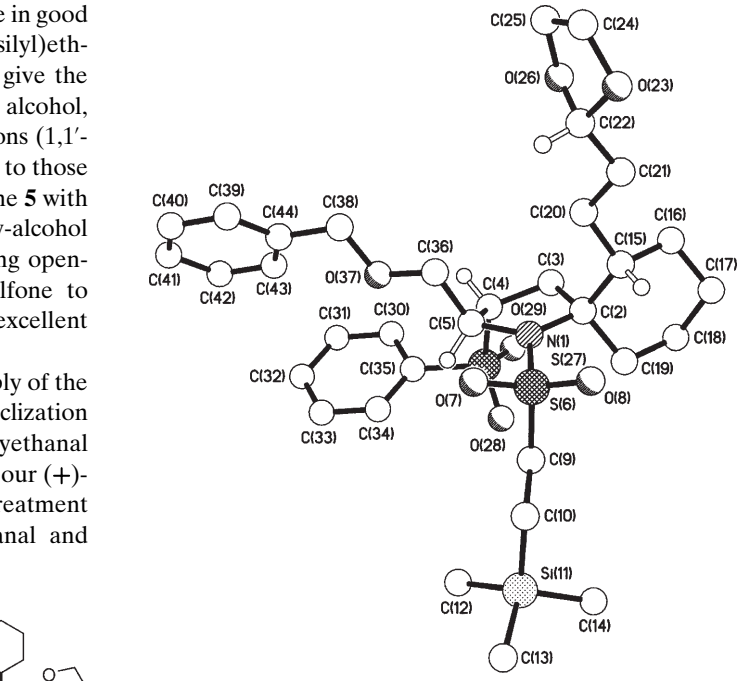
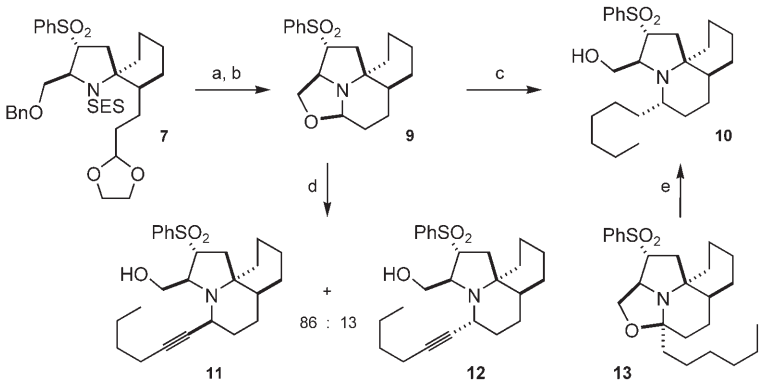


Figure 1. The molecular structure of **7**.

presumed intermediate iminium species. The steric bulk of the hexyl reagent appears to dominate the inherent stereoelectronic bias towards addition to the *Re* face. Evidence for the formation of the product of *Re*-face attack by a sterically less demanding nucleophile was provided by the virtually quantitative, completely stereoselective conversion of the hexyl-substituted homologue **13** into **10** upon treatment with $LiAlH_4$.[22] This problem was circumvented by replacing hexylmagnesium bromide with the sterically less demanding alkyne-containing C6 nucleophile hex-1-ynylmagnesium bromide in the reaction with **9**. In this case an S_N1-like substitution reaction occurred to give a separable 86:13 mixture of alkynes **11** and **12**. The structure of **11** was assigned conclusively by X-ray crystallographic analysis of its HCl salt (Figure 2).[21]

The conversion of the alkynyl side chain into the desired hexyl moiety required careful optimization of the catalyst



Scheme 4. a) nBu_4NF, THF, 97 %; b) BBr_3, CH_2Cl_2, 85 %; c) n-$C_6H_{13}MgBr$, THF, 0 °C, 79 %; d) n-$C_4H_9C{\equiv}CMgCl$, THF, 0 °C, 99 %; e) $LiAlH_4$, 99 %.

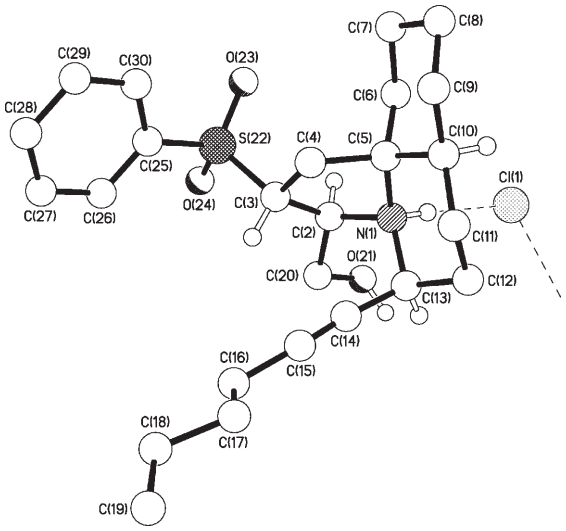
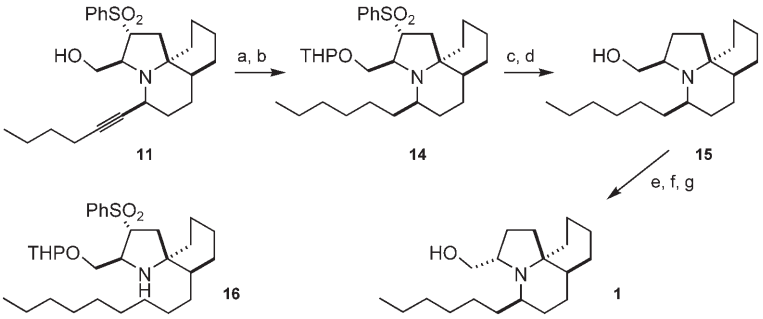


Figure 2. The molecular structure of **11**·HCl.

system and the substrate structure; the hydrogenolysis of the propargylic C–N bond was a major competing pathway for many of the catalysts studied. It was found eventually that quantitative THP protection of the primary alcohol functionality in **11** gave a substrate which underwent hydrogenation in ethyl acetate with H_2 (9 bar) and Pd on alumina to provide the THP ether **14** in 72% yield together with the overreduced pyrrolidine **16** (22%; Scheme 5). The phenylsulfonyl and THP groups were removed under standard conditions in



Scheme 5. a) DHP, PTSA, CH_2Cl_2, 100%; b) Pd/Al_2O_3, H_2 (9 bar), EtOAc, 72% (+ hydrogenolysis product **16**: 22%); c) Na, NH_3, Et_2O, 97%; d) PTSA, MeOH, 100%; e) Jones oxidation, then MeOH, conc. H_2SO_4; f) NaOMe, MeOH; g) $LiAlH_4$, Et_2O, 88% from **15**. DHP = 3,4-dihydro-2*H*-pyran, PTSA = *p*-toluenesulfonic acid, THP = tetrahydropyranyl.

virtually quantitative yield to give the primary alcohol **15**. Finally, the configuration at C3 was adjusted easily by conversion of the alcohol into the corresponding methyl ester, base-mediated epimerization, and reduction to give (±)-**1** in 88% yield from **15**. The ^1H and ^{13}C NMR spectroscopic data for racemic lepadiformine synthesized by this route were identical to those reported previously.[7d]

In summary, the synthesis of (±)-lepadiformine described herein demonstrates further the usefulness of the 5-*endo*-trig strategy for pyrrolidine synthesis, and highlights the compatibility of the SES nitrogen-protecting group with this mode of reactivity; in contrast, related *N*-tosyl compounds are not suitable substrates.[23] Ongoing research is directed towards the development of a short synthetic route to the aziridine **5** in enantiomerically pure form, with a view to its use in enantioselective syntheses of **1** and **2**. In particular, we plan to establish whether the introduction of a hexyl side chain through iminium-ion formation proceeds with the desired stereoselectivity when the C3 carbon atom with a hydroxymethyl substituent has the correct *S* configuration. The results of these studies will be reported in due course.

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[22] Substrate **13** was synthesized analogously to **9** by cyclization of a homologue of **6** with the hexyl side chain to give a homologue of pyrrolidine **7**, followed by acid-mediated cyclization. The exposure of **13** to other reducing agents ($NaBH_3CN$, $LiAlH_4$–$AlCl_3$) also resulted in the formation of **10** (100 and 61%, respectively).

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